PRE-OPERATIVE EVALUATION FOR CARDIAC AUTONOMIC NEUROPATHY AND THEIR BEHAVIOR DURING REGIONAL ANAESTHESIA

Dissertation submitted in partial fulfillment of

M.D. DEGREE EXAMINATION

M.D. ANESTHESIOLOGY AND CRITICAL CARE– BRANCH X.

GOVERNMENT KILPAUK MEDICAL COLLEGE, CHENNAI.

THE TAMILNADU Dr.M.G.R. MEDICAL UNIVERSITY

CHENNAI, TAMILNADU

APRIL 2011.

CERTIFICATE

This is to certify that this dissertation titled **"PRE-OPERATIVE EVALUATION FOR CARDIAC AUTONOMIC NEUROPATHY AND THEIR BEHAVIOR DURING REGIONAL ANAESTHESIA"** has been prepared by **Dr.S.SIVAKUMAR** under my supervision in the department of Anaesthesiology and critical care, Government Kilpauk Medical College, Chennai during the academic period 2008 – 2011 and is being submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the university regulation for the award of the Degree of Doctor of Medicine (M.D.Anaesthesiology and Critical Care) and his dissertation is a bonafide work.

Prof.Dr.KANAGASABAI,M.D
DEAN
Government Kilpauk Medical College & Hospital,
Chennai

Prof.Dr.P.S.SHANMUGAM,M.D.,D.A.,
PROFESSOR & HOD
Department of Anaesthesiology and Critical Care,
Government Kilpauk Medical College
Chennai & Hospital, Chennai.

ACKNOWLEDGEMENT

I wish to express my sincere thanks to Dr. V.Kanagasabai,M.D., Dean Government Kilpauk Medical College ,Chennai for having kindly permitted me to utilize the facilities of the hospital for the conduct of the study.

My heart felt thanks to my beloved Professor and Head of the Department of Anesthesiology and critical care, Government Kilpauk Medical College And Hospital Dr.P.S.Shanmugam,M.D.,D.A., for his motivation, valuable suggestions, constant supervision and for providing all necessary arrangements for conducting the study.

I also like to thank my Assistant Professors and tutors in anaesthesiology in Kilpauk Medical College for their support during my study period. I also like to thank my colleague postgraduates for their support. I also like here to thank the theatre staff and assistants for their co-operation in conducting the study.

I also like to thank the statistician Mr.Padmanabhan for his support in the statistic works. I wish to thank all the patients whose willingness and co-operation made this study successful.

CONTENTS

DECLARATION

I, Dr. S.Sivakumar, solemnly declare that the dissertation **"PRE-OPERATIVE EVALUATION FOR CARDIAC AUTONOMIC NEUROPATHY AND THEIR BEHAVIOR DURING REGIONAL ANAESTHESIA"** is a bonafide work done by me in the Department of Anaesthesiology and Critical care, Government Kilpauk, Medical College, Chennai under the able guidance of Prof. **Dr. P.S. Shanmugam, MD., DA.,** Professor and HOD, Department of Anaesthesiology and Critical care, Government Kilpauk Medical College, Chennai.

Place : Chennai

Date :

(**DR. S.SIVAKUMAR)**

INTRODUCTION

Cardiovascular autonomic neuropathy (CAN), a common form of autonomic dysfunction found in patients with diabetes mellitus, causes abnormalities in heart rate control, as well as defects in central and peripheral vascular dynamics. Individuals with parasympathetic dysfunction have a high resting heart rate most likely because of vagal neuropathy that results in unopposed increased sympathetic outflow. Persons with a combined parasympathetic/sympathetic dysfunction have slower heart rates. With advanced nerve dysfunction, heart rate is fixed. Thus, it is apparent that the determination of heart rate itself is not a reliable diagnostic sign of CAN. Reduction in variability of heart rate is the earliest indicator of CAN. Cardiovascular autonomic neuropathy occurs in ~17% of patients with type 1 diabetes and 22% of those with type 2. An additional 9% of type 1 patients and 12% of type 2 patients have borderline dysfunction. In a review of several epidemiological studies among individuals with diabetes, the 5-year mortality rate is five times higher for individuals with cardiovascular autonomic neuropathy than for individuals without cardiovascular autonomic involvement. The autonomic nervous system, which includes the parasympathetic and sympathetic systems, plays an important role in the regulation of myocardial function, heart rate, and myocardial blood flow. The sympathetic system innervates the myocardium via sympathetic nerve fibers

that traverse the subendocardium along the path of the coronary vessels, from the base to the apex of the heart. Extended increased stimulation of cardiac adrenergic receptors results in desensitization and downregulation of the receptors, as well as increased receptor degradation and decreased receptor synthesis. In diabetes, CAN is ultimately the result of complex interactions among degree of glycemic control, disease duration, age-related neuronal attrition, and systolic and diastolic blood pressure.

Hyperglycemia plays the key role in the activation of various biochemical pathways related to the metabolic and/or redox state of the cell, which, in concert with impaired nerve perfusion, contribute to the development and progression of diabetic neuropathies. Experimental data implicate a number of pathogenic pathways that may impact autonomic neuronal function in diabetes including: formation of advanced glycation end products, increased oxidative/nitrosative stress with increased free radical production, activation of the polyol and protein kinase C pathways, activation of poly ADP ribosylation, and activation of genes involved in neuronal damage .

Clinical Manifestations of Cardiovascular Autonomic Dysfunction

Exercise intolerance

In diabetic individuals with CAN, exercise tolerance is limited as a result of impaired parasympathetic/sympathetic responses that would

normally enhance cardiac output and result in directing peripheral blood flow to skeletal muscle.

Intra-operative cardiovascular liability:

There is a 2- to 3-fold increase in cardiovascular morbidity and mortality intra-operatively for patients with diabetes. Studies have demonstrated that the induction of anesthesia causes a greater degree of decline in heart rate and blood pressure in diabetic patients compared with non-diabetic individuals and that hemodynamic stability, in the intra-operative period, depends on the severity of autonomic dysfunction .

Orthostatic hypotension OH is characterized by a defect in this reflex arc, resulting in signs and symptoms such as weakness, faintness, dizziness, visual impairment, and syncope. Although the absolute fall in blood pressure is arbitrary, OH is usually defined as a fall in blood pressure [*i.e.* >20–30 mm Hg for systolic or >10 mm Hg for diastolic in response to postural change, from supine to standing.

Painless myocardial ischemia

Inability to detect ischemic pain can impair the recognition of myocardial ischemia or MI. The mechanisms of painless myocardial ischemia are, however, complex and not fully understood. Altered pain thresholds, sub threshold ischemia not sufficient to induce pain, and dysfunction of the afferent cardiac autonomic nerve fibers have all been

suggested as possible mechanisms .A recent investigation that used positron emission tomography to measure regional cerebral blood flow as an index of regional neuronal activation has shown that impaired afferent signaling resulting from autonomic dysfunction is associated with failed signal transmission from the thalamus to the frontal cortex .

Increased risk of mortality

Impaired autonomic control of heart rate is linked to increased risk of mortality. Reduced parasympathetic function or increased sympathetic activity may provide the propensity for lethal arrhythmias.

Measurement of Cardiovascular Autonomic Function

In the early 1970s, Ewing et al proposed five simple noninvasive cardiovascular reflex tests (Valsalva maneuver, heart rate response to deep breathing, heart rate response to standing up, blood pressure response to standing up, and blood pressure response to sustained handgrip) that have been applied successful. Today, sensitive and early assessment of cardiovascular autonomic neuropathy is possible by means of noninvasive autonomic function tests, including power spectral analysis of a series of successive R-R intervals (frequency domain analyses). This can be performed on short R-R sequences (e.g.,7 minute) or on 24-hour electrocardiogram recordings. The heart rate power spectrum is typically divided into two frequency bands: low (0.04 to 0.15 Hz) and high (0.15 to

0.4 Hz). The high-frequency region is generally considered a marker of vagal activity, whereas the low-frequency component is influenced by both sympathetic and vagal activity.

The association of mortality and cardiovascular autonomic dysfunction indicates that individuals with abnormal autonomic function tests are candidates for close surveillance. Thus it has been recommended that a baseline determination of cardiovascular autonomic function be performed upon diagnosis in type 2 diabetes and within 5 years of diagnosis for those with type 1 diabetes, followed by a yearly repeat test. In addition, the presence of autonomic dysfunction should alert the health care professional to search for associated risk factors of cardiovascular disease and implementation of an intense program to reduce these factors and thereby reduce the risk of mortality.

Treatment Interventions to Ameliorate Cardiovascular Autonomic Dysfunction via Pharmacological Agents

Interventions to ameliorate reduced HRV are being evaluated in clinical trials based on theories of the pathogenesis of diabetic neuropathy. Development of diabetic neuropathy is the result of a multifactorial process including metabolic insult to nerve fibers, neurovascular insufficiency, increased oxidative stress, reduction in neurotrophic growth factors, deficiency of essential fatty acids, formation of advanced glycosylation end

products, and autoimmune damage .Various pharmacological agents that are directed at components of the pathogenic process are described below.

Clinical assessment of cardiac autonomic nervous system

Clinical observation	Method of measurement	Normal value
I.parasympathetic nervous system		
*Heart rate response to valsalva	Patients' blows into a mouth piece maintaining a pressure of 40 mmHG for 15 seconds. The valsalva ratio is the ratio of the longest R-R interval on the ECG immediately after release to the shortest R-R interval during the maneuver.	Ratio > 1.21
*Heart rate response to standing	Heart rate is measured as the patient changes from supine to standing position (increase maximal around 15 th beat after standing and slowing maximal around 30 th beat).the response to standing is expressed as the 30:15 ratio and is the ratio of the longest R-R interval(around 30 th beat) to the shortest R-R interval (around 15 th beat).	Ratio >1.04
*Heart rate response to deep breathing	Patients take six deep breaths in 1 minute.the maximum and minimum heart rates during each cycle are measured and the mean of the differences (maximum heart rate-minimum heart rate) during three successive breathing cycles is taken as the maximum – minimum heart rate.	Mean difference >15 BPM
II. sympathetic system		
*Blood pressure response to standing	The patients changes from the supine to standing position and the standing systolic blood pressure is subtracted from the supine systolic blood pressure	Difference < 10 mmHG
*Blood pressure response to sustained handgrip	The patients maintain a hand grip of 30% of maximum squeeze for up to 5 minutes. The blood pressure is measured every minute and the initial diastolic blood pressure is subtracted from the diastolic blood pressure just prior to release	Difference >16 mmHG

Glycemic control

The results of the Diabetes Control and Complications Trial showed that intensive treatment prevented the development of abnormal RR variation and slowed the deterioration of autonomic dysfunction over time.

Antioxidants

During chronic hyperglycemia, the metabolism of glucose also results in the generation of free radicals.α-Lipoic acid, an antioxidant that reduces free radical formation, appears to slow progression of CAN. For persons with type 2 diabetes, the improvement in CAN was seen after 4 months of treatment with an oral dosage of 800 mg/d.

Angiotensin converting enzyme (ACE) inhibitors

In human diabetic neuropathy, impaired nerve blood flow has been demonstrated Given that vascular dysfunction may be part of the pathogenesis of diabetic neuropathy, ameliorating this abnormality may positively benefit nerve function. ACE inhibitors promote vasodilatation by preventing the generation of angiotensin II and by preventing the breakdown of bradykinin. Angiotensin II, in addition to its role as a vasoconstrictor, stimulates aldosterone release and promotes sympathetic outflow, thus ACE inhibitors may provide additional benefits as a result of the inhibition of angiotensin II.

Aldosterone blockers

Aldosterone has been shown to affect the autonomic nervous system with sympathetic activation and parasympathetic inhibition and impair the baroreflex response Other dysfunctions associated with aldosterone include the blockage of myocardial uptake of nor epinephrine in animal models and decreased arterial and venous compliance, leading to vascular organ damage Spironolactone, an aldosterone-receptor blocker, has been used to reduce the morbidity and mortality

Calcium-channel blockers

Although the mechanism by which verapamil influences HRV is not clear, it may be due to specific properties of the drug that have a suppressive effect on sympathetic outflow of catecholamines. Calcium-channel blockers may not, however, have a beneficial effect on HRV in persons with diabetes. For example, verapamil had no effect on HRV in diabetic subjects post-MI, whereas long-acting calcium antagonists enhanced, rather than reduced, sympathetic activity in patients with type 2 diabetes

ß-Blockers

The use of ß-blockers in diabetic patients has been questioned because these agents may mask signs and symptoms of hypoglycemia and interfere with insulin release. In the ß-blocker Heart Attack Trial, propranolol improved recovery of parasympathetic tone and decreased morning

sympathetic predominance for post-MI patients. The addition of metoprolol to ramipril-treated type 1 diabetic patients with abnormal albuminuria was also shown to improve autonomic dysfunction

Metformin

Free fatty acids (FFAs) interfere with glucose metabolism .Under normal circumstances, FFAs are the main fuel source for the heart .Recently, it has been shown that the combination of TNF-α and hyperglycemia stimulated lipolysis with a consequential increase in FFAs and induced insulin resistance .Decreased activation of the parasympathetic nervous system increases lipolysis, thus resulting in an increased concentration of FFAs in the plasma .An increase in FFAs has been shown to affect the cardiovascular system through activation of the sympathetic nervous system in healthy subjects ,as well as in individuals with type 2 diabetes .Recently, it was demonstrated that overweight type 2 diabetic patients had metformin-related decreases in FFAs and insulin resistance that were associated with improved sympathovagal balance .

Treatment Interventions to Ameliorate Cardiovascular Autonomic Dysfunction via Nonpharmacological Agents

It is well known that exercise plays an important role in the treatment of diabetes. The role of exercise in the improvement of cardiovascular autonomic function is not as clear. Endurance training was also shown to

improve vagal activity in nondiabetic patients who had a MI (and in insulin-requiring diabetic individuals with early CAN other studies showed no benefit or only minimal benefit for healthy men and individuals with type 2 diabetes.

Investigational Medications for Potential Use for Cardiovascular Autonomic Dysfunction

Aldose reductase inhibitors

Chronic hyperglycemia causes activation of the polyol pathway with the accumulation of sorbitol and fructose, resulting in various metabolic imbalances that lead to neuronal dysfunction In the early 1980s, aldose reductase inhibitors (ARIs), which reduce activity in the polyol pathway, generated hope with regard to the potential treatment of diabetic neuropathy. Due to lack of safety and/or efficacy, however, several ARIs have been withdrawn from the market and currently no ARIs are available for use in the U.S. One ARI (*i.e.* epalrestat) has been marketed in Japan since 1995. Whereas two studies have shown improved measures of CAN with epalrestat administration another study showed no effect of epalrestat on cardiac sympathetic dysfunction. Newer agents such as fidarestat and AS-3201 are being investigated in ongoing clinical trials assessing peripheral neuropathy.

AIM OF THE STUDY

This study aimed on Pre-operative evaluation for diabetic autonomic neuropathy using CANS 504 (cardiac autonomic neuropathy system analyzer) and their behavior during regional anesthesia.

Inclusion criteria:

Case:

- Age: 40- 60 years.
- Sex: both male and female.
- Diabetes mellitus > 3 years
- PS II & III

Control:

- Age: 40- 60 years.
- Sex: both male and female.
- Not a known diabetes mellitus
- PS I

Exclusion criteria:

- age < 40 & >60 years.
- PS IV

Equipments required:

- CANS 504 – cardiac autonomic neuropathy system analyzer.
- ECG monitor
- Sphygmomanometer.
- pulse oxymeter.

ANATOMY AND PHYSIOLOGY OF ANS

Langley (1852-1925) coined the term autonomic nervous system.ANS innervation is divided into sympathetic nervous system and parasympathetic nervous system divisions. The sympathetic division has thoracolumbar "outflow", meaning that the neurons begin at the thoracic and lumbar (T1-L2) portions of the spinal cord. The parasympathetic division has craniosacral "outflow", meaning that the neurons begin at the cranial nerves (CN 3, CN7, CN 9, CN10) and sacral (S2-S4) spinal cord.

The ANS is unique in that it requires a sequential two-neuron efferent pathway; the preganglionic neuron must first synapse onto a postganglionic neuron before innervating the target organ. The preganglionic, or first, neuron will begin at the "outflow" and will synapse at the postganglionic, or second, neuron's cell body. The post ganglionic neuron will then synapse at the target organ.

Anatomy

Sympathetic division

The sympathetic division (thoracolumbar outflow) consists of cell bodies in the lateral horn of spinal cord (intermediolateral cell columns) of the spinal cord from T1 to L2. These cell bodies are GVE neurons (general visceral efferent), and are the preganglionic neurons. There are several

locations upon which preganglionic neurons can synapse for their postganglionic neurons:

- Paravertebral ganglia of the sympathetic chain (these run on either side of the vertebral bodies)
- Prevertebral ganglia (celiac ganglia, superior mesenteric ganglia, inferior mesenteric ganglia)
- Chromaffin cells of adrenal medulla (this is the one exception to the two-neuron pathway rule: synapse is direct onto cell bodies)

These ganglia provide the postganglionic neurons from which innervation of target organs follows. Examples of splanchnic (visceral) nerves are:

- Cervical cardiac nerves & thoracic visceral nerves which synapse in the sympathetic chain
- Thoracic splanchnic nerves (greater, lesser, least) which synapse in the prevertebral ganglion
- Lumbar splanchnic nerves which synapse in the prevertebral ganglion
- Sacral splanchnic nerves which synapse in the inferior hypogastric plexus

These all contain afferent (sensory) nerves as well, also known as GVA neurons (general visceral afferent).

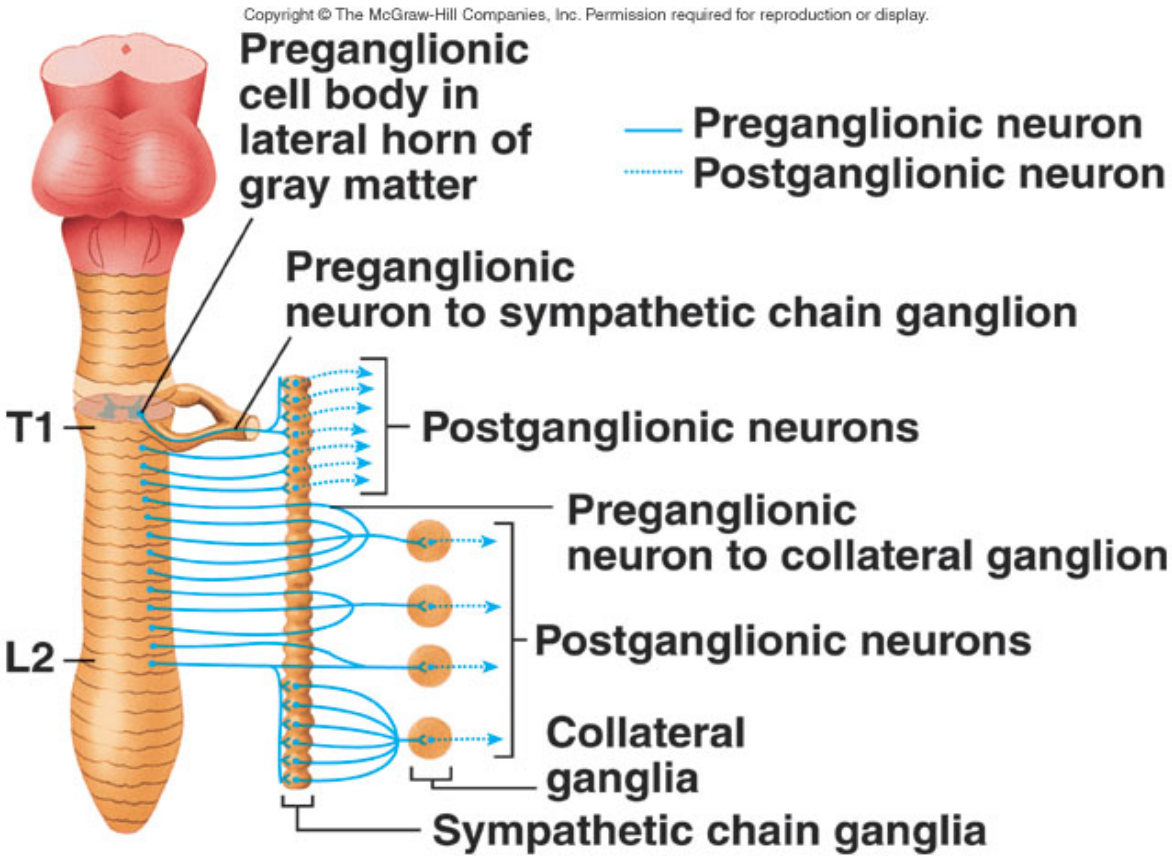
Parasympathetic division

The parasympathetic division (craniosacral outflow) consists of cell bodies from one of two locations: brainstem (Cranial Nerves 3, 7, 9, 10) or sacral spinal cord (S2, S3, S4). These are the preganglionic neurons, which synapse with postganglionic neurons in these locations:

- Parasympathetic ganglia of the head (Ciliary (CN3), Submandibular (CN7), Pterygopalatine (CN7), Otic (CN9))
- In or near wall of organ innervated (Vagus (CN10), Sacral nerves (S2, S3, S4))

These ganglia provide the postganglionic neurons from which innervations of target organs follows. Examples are:

- The preganglionic parasympathetic splanchnic (visceral) nerves
- Vagus nerve, which wanders through the thorax and abdominal regions innervating, among other organs, the heart, lungs, liver and stomach



Sensory neurons

The sensory arm is made of "primary visceral sensory neurons" found in the peripheral nervous system (PNS), in "cranial sensory ganglia": the geniculate, petrosal and nodose ganglia, appended respectively to cranial nerves VII, IX and X. These sensory neurons monitor the levels of carbon dioxide, oxygen and sugar in the blood, arterial pressure and the chemical composition of the stomach and gut content. (They also convey the sense of taste, a conscious perception). Blood oxygen and carbon dioxide are in fact directly sensed by the carotid body, a small collection of chemosensors at the bifurcation of the carotid artery, innervated by the petrosal (IXth) ganglion.

Primary sensory neurons project (synapse) onto "second order" or relay visceral sensory neurons located in the medulla oblongata, forming the nucleus of the solitary tract (nTS), that integrates all visceral information. The nTS also receives input from a nearby chemosensory center, the area postrema, that detects toxins in the blood and the cerebrospinal fluid and is essential for chemically induced vomiting or conditional taste aversion (the memory that ensures that an animal which has been poisoned by a food never touches it again). All these visceral sensory information's constantly and unconsciously modulate the activity of the motor neurons of the ANS

Motor neurons

Motor neurons of the ANS are also located in ganglia of the PNS, called "autonomic ganglia". They belong to three categories with different effects on their target organs (see below "Function"): sympathetic, parasympathetic and enteric.

Sympathetic ganglia are located in two sympathetic chains close to the spinal cord: the prevertebral and pre-aortic chains. Parasympathetic ganglia, in contrast, are located in close proximity to the target organ: the submandibular ganglion close to salivary glands, paracardiac ganglia close to the heart etc... Enteric ganglia, which as their name implies innervate the digestive tube, are located inside its walls and collectively contain as many neurons as the entire spinal cord, including local sensory

neurons, motor neurons and interneurons. It is the only truly autonomous part of the ANS and the digestive tube can function surprisingly well even in isolation. For that reason the enteric nervous system has been called “the second brain”.

The activity of autonomic ganglionic neurons is modulated by “preganglionic neurons” (also called improperly but classically "visceral motoneurons") located in the central nervous system. Preganglionic sympathetic neurons are in the spinal cord, at thoraco-lumbar levels. Preganglionic parasympathetic neurons are in the medulla oblongata (forming visceral motor nuclei: the dorsal motor nucleus of the vagus nerve (dmnX), the nucleus ambiguus, and salivatory nuclei) and in the sacral spinal cord. Enteric neurons are also modulated by input from the CNS, from preganglionic neurons located, like parasympathetic ones, in the medulla oblongata (in the dmnX).

The feedback from the sensory to the motor arm of visceral reflex pathways is provided by direct or indirect connections between the nucleus of the solitary tract and visceral motoneurons.

Function

Sympathetic and parasympathetic divisions typically function in opposition to each other. But this opposition is better termed complementary

in nature rather than antagonistic. Consider sympathetic as "fight or flight" and parasympathetic as "rest and digest".

Sympathetic nervous system

Promotes a "fight or flight" response, corresponds with arousal and energy generation, and inhibits digestion.

- Diverts blood flow away from the gastro-intestinal (GI) tract(α1) and skin(α1 α2) via vasoconstriction.
- Blood flow to skeletal muscles (α1,β2) and the lungs(α1,β2) is enhanced (by as much as 1200% in the case of skeletal muscles).
- Dilates bronchioles of the lung (β2), which allows for greater alveolar oxygen exchange.
- Increases heart rate and the contractility of cardiac cells (β1,β2) (myocytes), thereby providing a mechanism for the enhanced blood flow to skeletal muscles.
- Dilates pupils (α1) and relaxes the ciliary muscle to the lens (β2), allowing more light to enter the eye and far vision.\
- Provides vasodilation for the coronary vessels of the heart (β2).
- Constricts all the intestinal sphincters (α1) and the urinary sphincter (α1).
- Inhibits peristalsis (α1, α2, β2).
- Stimulates orgasm (α1).

- Glucose released into blood from liver(α1,β2) ,breakdown of glycogen to glucose in skeletal muscle (β2)
- Fat breakdown and release of fatty acids(β3)

Parasympathetic nervous system

Promotes a "rest and digest" response, promotes calming of the nerves return to regular function, and enhances digestion (m receptors).

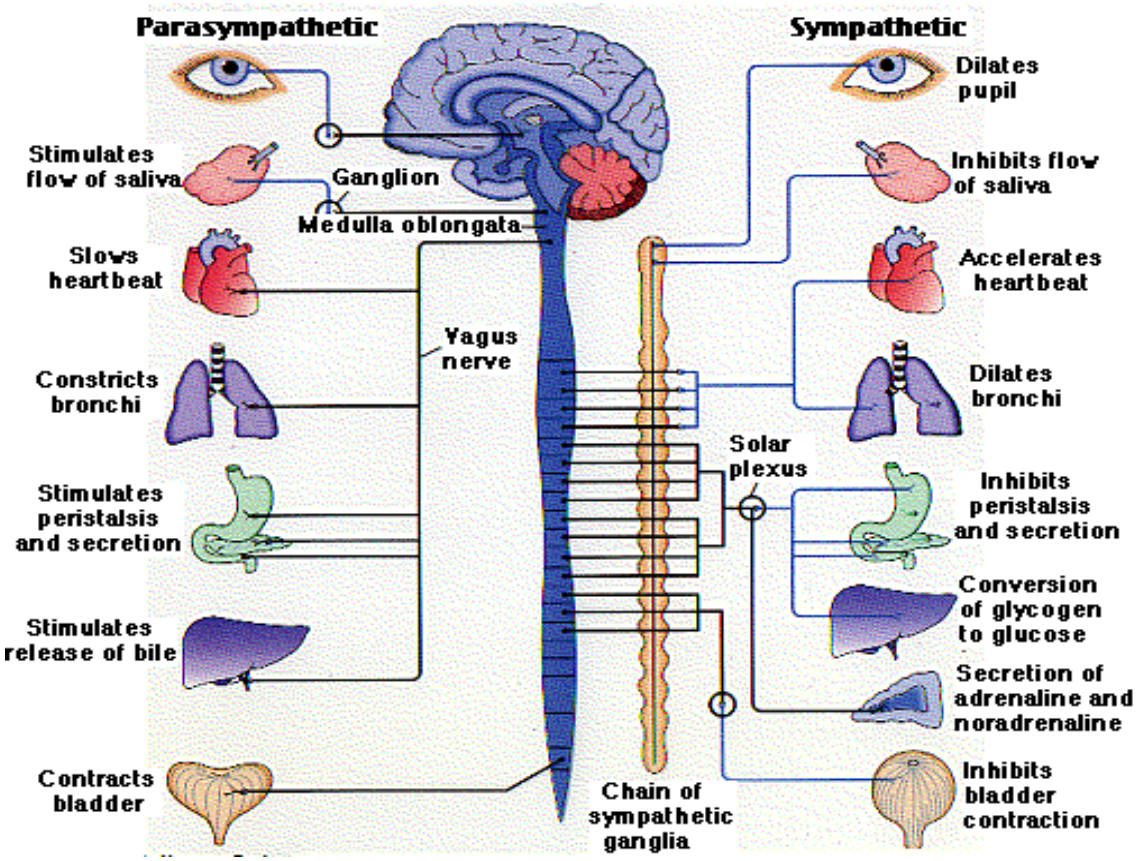
- Dilates blood vessels leading to the GI tract, increasing blood flow. This is important following the consumption of food, due to the greater metabolic demands placed on the body by the gut.
- The parasympathetic nervous system can also constrict the bronchiolar diameter when the need for oxygen has diminished.
- Dedicated cardiac branches of the Vagus and thoracic Spinal Accessory nerves impart Parasympathetic control of the Heart or Myocardium.
- During accommodation, the parasympathetic nervous system causes constriction of the pupil and contraction of the ciliary muscle to the lens, allowing for closer vision.
- The parasympathetic nervous system stimulates salivary gland secretion, and accelerates peristalsis, so, in keeping with the rest and digest functions, appropriate PNS activity mediates digestion of food and indirectly, the absorption of nutrients.

- Is also involved in erection of genitals, via the pelvic splanchnic nerves 2–4.
- Stimulates sexual arousal.

Neurotransmitters and pharmacology

At the effector organs, sympathetic ganglionic neurons release noradrenalin (norepinephrine), along with other cotransmitters such as ATP, to act on adrenergic receptors, with the exception of the sweat glands and the adrenal medulla:

- Acetylcholine is the preganglionic neurotransmitter for both divisions of the ANS, as well as the postganglionic neurotransmitter of parasympathetic neurons. Nerves that release acetylcholine are said to be cholinergic. In the parasympathetic system, ganglionic neurons use acetylcholine as a neurotransmitter, to stimulate muscarinic receptors.
- At the adrenal cortex, there is no postsynaptic neuron. Instead the presynaptic neuron releases acetylcholine to act on nicotinic receptors.
- Stimulation of the adrenal medulla releases adrenaline (epinephrine) into the bloodstream which will act on adrenoceptors, producing a widespread increase in sympathetic activity


Parasympathetic
Sympathetic
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Vagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction

PHARMACOLOGY

Dopamine

Dopamine is a neurotransmitter activating dopamine receptors. The hypothalamus also releases it as a neurohormone, with its main function the inhibition of prolactin release from the anterior pituitary lobe. Dopamine is available as an intravenous medication acting on the sympathetic nervous system, producing effects such as increased heart rate and blood pressure. Increased dopamine can improve the symptoms of people with Parkinson's disease and other related disorders; however, dopamine itself cannot cross the blood-brain barrier, so injecting or ingesting it does not get it to the brain. Instead, a synthetic L-DOPA, which is a precursor to dopamine that does cross the blood-brain barrier, can be used

History:

Dopamine was first synthesized in 1910 by George Barger and James Ewens at Wellcome Laboratories in London, England. Dopamine's function as a neurotransmitter was first recognized in 1958 by Arvid Carlsson and Nils-Åke Hillarp at the Laboratory for Chemical Pharmacology of the National Heart Institute of Sweden.

Synthesis

Dopamine is a member of the catecholamine family, and is a precursor to epinephrine (or adrenaline) and norepinephrine (noradrenaline).

Dopamine is synthesized by the decarboxylation of DOPA by aromatic-L-amino-acid decarboxylase.

Inactivation and degradation

Two major degradation pathways for dopamine exist. In most areas of the brain, including the striatum and basal ganglia, dopamine is inactivated by reuptake via the dopamine transporter (DAT1), then enzymatic breakdown by monoamine oxidase (MAOA and MAOB) into 3,4-dihydroxyphenylacetic acid. In the prefrontal cortex, however, there are very few dopamine transporter proteins, and dopamine is instead inactivated by reuptake via the norepinephrine transporter (NET), presumably on neighboring norepinephrine neurons, then enzymatic breakdown by catechol-O-methyl transferase (COMT) into 3-methoxytyramine.

Therapeutic Uses

Dopamine acts upon receptors present on immune cells, with all subtypes of dopamine receptors found on Levodopa is a dopamine precursor used in various forms to treat Parkinson's disease and dopa-responsive dystonia.

Peripheral effects

Dopamine also has effects when administered through an IV line outside the central nervous system. The brand name of this preparation is known as Intropin. The effects in this form are dose dependent.

- Dosages from 2 to 5 μg/kg/min are considered the "renal dose." At this low dosage, dopamine binds D1 receptors, dilating blood vessels, increasing blood flow to renal, mesenteric, and coronary arteries; and increasing overall renal perfusion. Dopamine therefore has a diuretic effect, potentially increasing urine output from 5 ml/kg/hr to 10 ml/kg/hr
- Intermediate dosages from 5 to 10 μg/kg/min additionally have a positive inotropic and chronotropic effect through increased β1 receptor activation. It is used in patients with shock or heart failure to increase cardiac output and blood pressure. Dopamine begins to affect the heart at the lower doses, from about 3 μg/kg/min IV.
- High doses from 10 to 20 μg/kg/min is the "presser" dose. This dose causes vasoconstriction, increases systemic vascular resistance, and increases blood pressure through α1receptor activation; but can cause the vessels in the kidneys to constrict to the point where they will become non-functional

Renal effects

Dopamine induces natriuresis (sodium loss) in the kidneys.

Ephedrine

Ephedrine is a sympathomimetic amine commonly used as a stimulant, appetite suppressant, concentration aid, decongestant, and to treat hypotension associated with anesthesia. Nagayoshi Nagai, a Japanese chemist, was the first person to isolate ephedrine from Ephedra distachya (syn. Ephedra vulgaris) in 1885.

Mechanism of action

Ephedrine is a sympathomimetic amine. The principal mechanism of its action relies on its indirect stimulation of the adrenergic receptor system, which is part of the sympathetic nervous system (*SNS*), by increasing the activity of noradrenaline at the post-synaptic α- and β-receptors.

Indications

Both ephedrine and pseudoephedrine act as a bronchodilator, but pseudoephedrine has considerably less effect. Both also increase blood pressure, with again pseudoephedrine being considerably less effective popular supplement taken by body builders to cut down body fat before a competition. For many years, the US Coast Guard recommended ephedrine together with an equal 25 mg dose of promethazine to its sailors to combat seasickness.

Adverse effects

Adverse drug reactions (ADRs) are more common with systemic administration (e.g. injection or oral administration) compared to topical administration (e.g. nasal instillations). ADRs associated with ephedrine therapy include: Cardiovascular: tachycardia, cardiac arrhythmias, angina pectoris, vasoconstriction with hypertension Dermatological: flushing, sweating, acne vulgaris Gastrointestinal: anorexia, nausea Genitourinary: decreased urination due to vasoconstriction of renal arteries. Also, difficulty urinating is not uncommon, as alpha-agonists such as ephedrine constrict the internal urethral sphincter, mimicking the effects of sympathetic nervous system stimulation. Nervous system: restlessness, confusion, insomnia, mild euphoria, mania/hallucinations (rare except in previously existing psychiatric conditions), delusions, formication (may be possible, but lacks documented evidence) paranoia, hostility, panic, agitation Respiratory : dyspnea, pulmonary edema Miscellaneous : dizziness, headache, tremor, hyperglycemic reactions, dry mouth The neurotoxicity of 1-Ephedrine is disputed.

Contraindications

Ephedrine should not be used in conjunction with certain antidepressants, namely SNRIs (serotonin-norepinephrine re-uptake inhibitors), as this increases the risk of the above symptoms due to excessive

serum levels of norepinephrine. Ephedrine should be used with caution in patients with inadequate fluid replacement, impaired adrenal function, hypoxia, hypercapnia, acidosis, hypertension, hyperthyroidism, pro static hypertrophy,diabetes mellitus, cardiovascular disease, during delivery if maternal BP > 130/80 mmHg, and lactation.

Contraindications for the use of ephedrine include: closed angle glaucoma, phaeochromocytoma, asymmetric hypertrophy (idiopathic hypertrophic subaortic stenosis), concomitant or recent (previous 14 days) monoamine oxidase inhibitor (MAOI) therapy, general anaesthesia with halogenated hydrocarbons (particularly halothane), tachyarrhythmias or ventricular fibrillation, hypersensitivity to ephedrine or other stimulants. Ephedrine should not be used at any time during pregnancy unless specifically indicated by a qualified physician and only when other options are unavailable.

Recreational and illicit use

Anecdotal reports have suggested that ephedrine helps studying, thinking, or concentrating to a greater extent than caffeine. Some students and some white-collar workers have used ephedrine (or Ephedra-containing herbal supplements) for this purpose, as well as some professional athletes and weightlifters.

Atropine

Atropine is a tropane alkaloid extracted from deadly nightshade (Atropabelladonna), jimsonweed (*Daturastramonium*), mandrake (*Mandrag ora officinarum*) and other plants of the family Solanaceae

Natural sources

Atropine is found in many members of the Solanaceae family. The most commonly-found sources are Atropa belladonna, Datura inoxia, D metel, and D. stramonium. Other sources include members of the *Brugmansia* and *Hyoscyamus* genera. The *Nicotiana* genus (including the tobacco plant, *N. tabacum*) is also found in the Solanaceae family, but these plants do not contain atropine or other tropane alkaloids

Synthesis

Atropine can be synthesized by the reaction of tropine with tropic acid in the presence of hydrochloric acid. Chemistry and pharmacology Atropine is a racemic mixture of D-hyoscyamine and L-hyoscyamine, with most of its physiological effects due to L-hyoscyamine. Its pharmacological effects are due to binding to muscarinic acetylcholine receptors. It is an antimuscarinic agent.

Physiological effects and uses

Atropine increases firing of the sinoatrial node (SA) and conduction through the atrioventricular node (AV) of the heart, opposes the actions of

the vagus nerve, blocks acetylcholine receptor sites, and decreases bronchial secretions. In general, atropine lowers the parasympathetic activity of all muscles and glands regulated by the parasympathetic nervous system. This occurs because atropine is a competitive antagonist of the muscarinic acetylcholine receptors (acetylcholine being the main neurotransmitter used by the parasympathetic nervous system), therefore, it may cause swallowing difficulties and reduced secretions.

Ophthalmic use

Topical atropine is used as a cycloplegic, to temporarily paralyze the accommodation reflex, and as a mydriatic, to dilate the pupils.

Resuscitation

Injections of atropine are used in the treatment of bradycardia (an extremely low heart rate), asystole and pulseless electrical activity (PEA) in cardiac arrest. This works because the main action of the vagus nerve of the parasympathetic system on the heart is to decrease heart rate. Atropine blocks this action and, therefore, may speed up the heart rate. The usual dosage of atropine in bradyasystolic arrest is 0.5 to 1 mg IV push every three to five minutes, up to a maximum dose of 0.04 mg/kg. For symptomatic bradycardia, the usual dosage is 0.5 to 1.0 mg IV push, may repeat every 3 to 5 minutes up to a maximum dose of 3.0 mg

Atropine is also useful in treating second-degree heart block Mobitz Type 1 (Wenckebach block), and also third-degree heart block with a high Purkinje or AV-nodal escape rhythm. in the heart, but atropine inhibits this action.

Secretions and bronchoconstriction

Atropine's actions on the parasympathetic nervous system inhibits salivary, sweat, and mucus glands. This can be useful in treating hyperhidrosis, and can prevent the death rattle of dying patients.

Treatment for organophosphate poisoning

Atropine is not an actual antidote for organophosphate poisoning. However, by blocking the action of acetylcholine at muscarinic receptors, atropine also serves as a treatment for poisoning byorganophosphate insecticides and nerve gases, such as Tabun (GA), Sarin (GB), Soman (GD) and VX..

Optical penalisation

In refractive and accommodative amblyopia, when occlusion is not appropriate sometimes atropine is given to induce blur in the good eye.

Side-effects and overdose

Adverse reactions to atropine include ventricular fibrillation, supraventricular or ventricular tachycardia, dizziness, nausea, blurred vision, loss of balance, dilated pupils, photophobia, dry mouth and potentially

extreme confusion,dissociative hallucinations and excitation especially amongst the elderly.

Although atropine treats bradycardia (slow heart rate) in emergency settings, it can cause paradoxical heart rate slowing when given at very low doses, presumably as a result of central action in the CNS. Atropine is incapacitating at doses of 10 to 20 mg per person. Its LD_{50} is estimated to be 453 mg per person (per oral) with a probit slope of 1.8. The antidote to atropine is physostigmine orpilocarpine.

A common mnemonic used to describe the physiologic manifestations of atropine overdose is: "hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter". These associations reflect the specific changes of warm, dry skin from decreased sweating, blurry vision, decreased sweating/lacrimation, vasodilation, and central nervous system effects on muscarinic receptors, type 4 and 5. This set of symptoms is known as anticholinergic toxidrome, and may also be caused by other drugs with anticholinergic effects, such as diphenhydramine, phenothiazine antipsychotics and benztropine.

REVIEW OF LITERATURE

1. **Cardiovascular autonomic dysfunction and hemodynamic response to anesthetic induction in patients with coronary artery disease and diabetes mellitus**

Cornelius keyl ,M.D, and et al

Pre operative evaluation for cardiac autonomic neuropathy with spectral analysis of blood pressure and heart rate variability done for 60 patients scheduled for coronary artery surgery , 30 suffering from diabetes . Heart rate and blood pressure before anesthetic induction and before and after tracheal intubation were compared between groups. There was no relationship between cardiovascular autonomic function and hemodynamic behavior during anesthetic induction. These findings indicate that increased hemodynamic instability during anesthetic induction is not obligatory in patients with diabete mellitus and autonomic dysfunction.

2. Diabetic autonomic neuropathy : abnormal cardiovascular reaction under general anesthesia

Knuttgen d.weidemann d, doehn m

The influence of diabetic autonomic neuropathy upon the behavior of the circulatory system was investigated in 56 patients who had undergone ophthalmological surgery. During general anesthesia patients with diabetes experienced hypotensive reactions more often than non diabetes patients.

3. Diabetes-Induced Cardiac Autonomic Neuropathy

Scott W. Harden

This review outlines the relationship between diabetes mellitus and autonomic neuropathy, with special emphasis on the neurophysiological pathology of the cardiovascular system caused by this deadly epidemic. The high prevalence of diabetes combined with its association with cardiac autonomic neuropathy and the current lack of effective treatment options makes diabetic cardiac autonomic neuropathy a serious threat to a large portion of the human population.

4. A non-invasive approach to cardiac autonomic neuropathy in patients with diabetes mellitus

F. Weise, F. Heydenreich

Ten insulin-dependent diabetic patients (29 ± 2 years) with a short to moderately long duration of diabetes (11 ± 1 years) and cardiac vagal neuropathy based on measurements of respiratory sinus arrhythmia were compared to 10 healthy volunteers (27 ± 1 years) before and after the administration of atropine and atropine plus propranolol. There was no significant difference between diabetics and controls after combined autonomic blockade. It was concluded that heart rate spectral power could serve as an indirect, non-invasive, quantitative and sensitive marker of early cardiac sympathetic damage.

5. Cardiac autonomic and peripheral neuropathy in newly diagnosed type 2 diabetic patients

GR Kurashvili, RB Kurashvili, MG Khelashvili, LR Tsutskiridze, EL Shelestova & MN Kobaidze

At diagnosis 20–30% of patients (pts) with type2 diabetes (T2DM) have neuropathy, that often goes unrecognized. 39 pts with newly diagnosed T2DM without known CV disease, ketoacidosis, alcoholism and/or chronic liver disease and non-diabetic nerve damages, not taking medications affecting CAN reflex tests. Ewing's standard reflex tests were performed, severity of CAN was evaluated according to Jermendy, 1995. Standardized evaluation was conducted (Neurometer, Baltimore, MD), that discriminates between neuropathic and non-neuropathic pts and tests different nerve fiber types. CAN was observed in 53.85% of the patients; peripheral sensory dysfunction prevalence here was higher (35.9%), than in general population

.

METHODOLOGY

A randomized controlled, prospective comparative study was done to compare the behavior of diabetic patient with cardiac autonomic neuropathy and non-diabetic patient without cardiac autonomic neuropathy during spinal anesthesia. The study was conducted after approval by the hospital ethical committee and an informed written consent was obtained from all. The sympathetic nervous system is stimulated in the early stages of diabetes and extended exposure of the adrenergic receptors to increased cathecalomines level together with hyperglycemic and insulin deficiency is believed to cause diabetic CAN. An imbalance of sympathetic and parasympathetic control of cardiac function can lead to silent myocardial ischemia, sudden cardiac death due to lethal arrhythmias, orthostatic hypotension, resting tachycardia, decreased baroreceptor sensitivity, exercise intolerance diastolic dysfunction and B.P invariability (sztajzel ,2004). There is a 2-3 fold increase in cardiovascular morbidity and mortality intra-operatively for patient with diabetes

Noninvasive diagnostic methods assessing autonomic function allow identification of at risk patient pre-operatively and better prepare the anesthesiologist for potential hemodynamics. This study aimed to evaluate the diabetic patient and control group pre-operatively for cardiac autonomic neuropathy with CANS – 504 (cardiac autonomic neuropathy system

analyzer). A total number of 50 ASA II & III patients belonging to age group of 40 –60 years were divide into three groups 20 ,10, 20 respectively. Group I – patients with diabetic mellitus having cardiac autonomic neuropathy, group II –diabetic patient without cardiac autonomic neuropathy and group III –control patients non-diabetic without cardiac autonomic neuropathy. Those patients < 40 years and > 60 years & those of ASA IV were excluded from the study. Both male and females with diabetes mellitus more than 3 years are included in the case study.

Along with routine investigations, pre operative evaluation for cardiac autonomic neuropathy is done with CANS 504 (cardiac autonomic neuropathy system analyzer). CANS 504 is an important tool to measure and diagnose autonomic dysfunction using ECG R-R interval and automatic B.P measurement.

Understanding controls:

1. 3 lead ECG
2. B.P cuff
3. valsalva probe
4. spring loaded hand grip device

CANS – 504

Operating instruction :

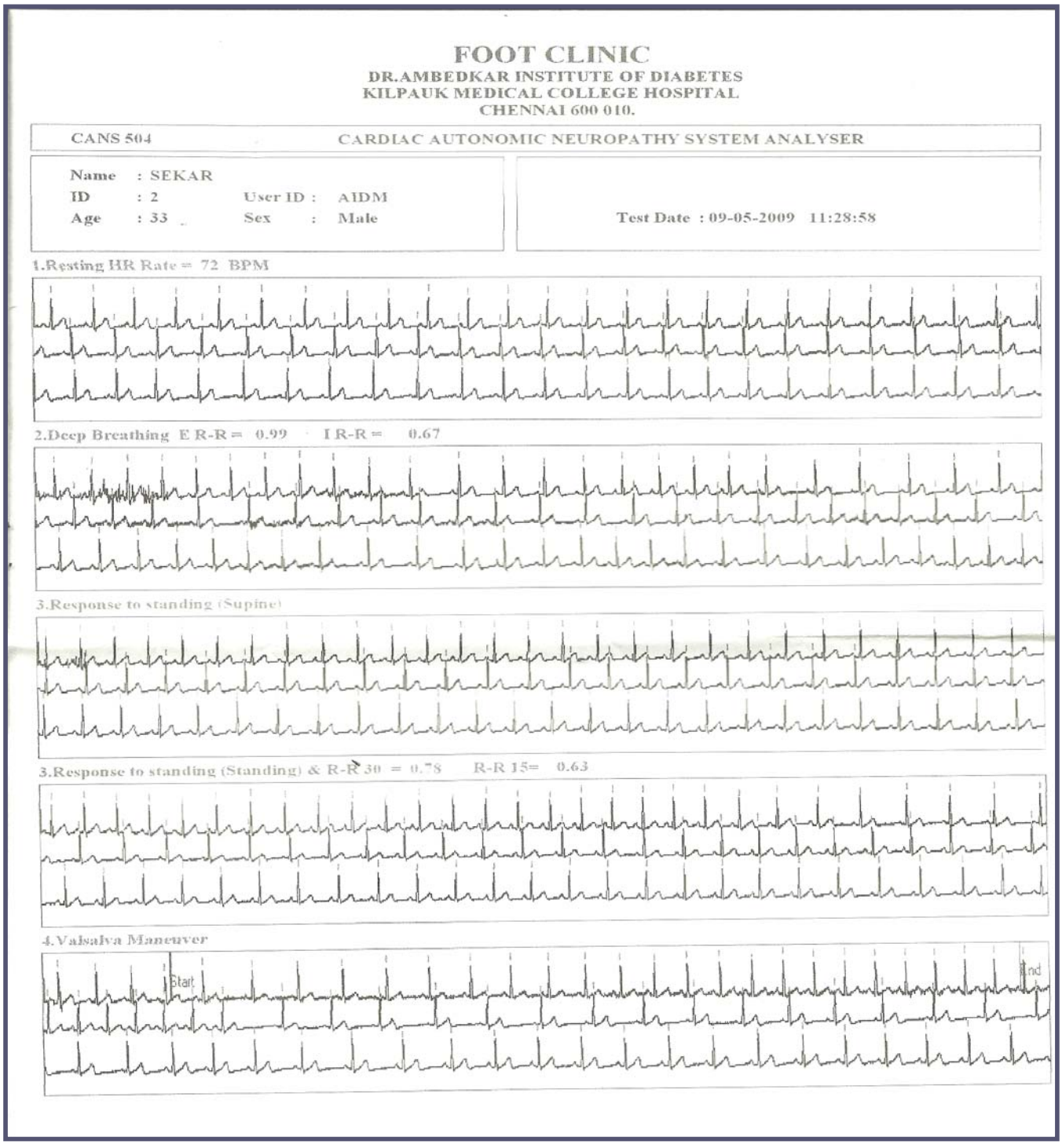
CANS 504 is connected to the PC through RS 232 serial communication. After connecting all accessories to the unit, patient should be in supine position. Attach ECG electrodes and record resting ECG,deep breathing ECG, supine ECG, valsalva ECG. B.P cuff attached to the patient .then record supine B.P, standing B.P, hand grip B.P (before hand grip and after 5 min.of 30 % hand grip).

Normal and abnormal values in autonomic study

TEST	**normal**	**borderline**	**abnormal**
1.**parasympathetic**:			
Valsalva	1.2	1.1– 1.2	1.1
Deep breathing [max:min hr]	15 BPM	11 –14 BPM	10 BPM
Standing	1.04	1.01 – 1.03	1.00
2.Sympathetic [b.p response] standing(systolic)	10 mmHg	11- 29 mmHg	30mmHg
Exercise(diastolic)	16 mmHg	11- 15 mmHg	10mmHg

Under aseptic precaution, subarachanoid block given at L2 –L3 level, volume 3 ml of 0.5% bupivacine given. Sensory level obtained up to T4-T5 level. Intra – operative recording of ECG rate and rhythm, B.P, pulse rate were done for each 5 minutes in first 30 minutes and then for each 15 minutes till the end of surgery. Injection ephedrine 6mg given i.v if systolic B.P falls below 90mmHg or 20% of baseline values. Injection atropine 0.6 mg given i.v pulse rate falls below 60/min.

Print out results of autonomic study using CANS 504



FOOT CLINIC
DR.AMBEDKAR INSTITUTE OF DIABETES
KILPAUK MEDICAL COLLEGE HOSPITAL
CHENNAI 600 010.

CANS 504 CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER

Name : SEKAR
ID : 2 User ID : AIDM
Age : 33 Sex : Male

Test Date : 09-05-2009 11:28:58

1.Resting HR Rate = 72 BPM

2.Deep Breathing E R-R = 0.99 I R-R = 0.67

3.Response to standing (Supine)

3.Response to standing (Standing) & R-R 30 = 0.78 R-R 15= 0.63

4.Valsalva Maneuver

Start

End

Print out results of autonomic study using CANS 504

FOOT CLINIC
DR.AMBEDKAR INSTITUTE OF DIABETES
KILPAUK MEDICAL COLLEGE HOSPITAL
CHENNAI 600 010.

CANS 504 — **CARDIAC AUTONOMIC NEUROPATHY SYSTEM ANALYSER**

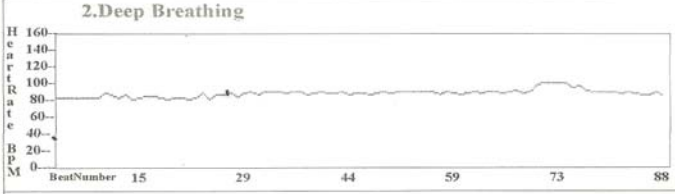
Name : KUMUTHA
ID : 5 User ID : 3372
Age : 43 Sex : Female
Referal : DR. C.R. ANAND MOSES

Test Date : 20-05-2009 11:34:10

PARASYMPATHETIC FUNCTION

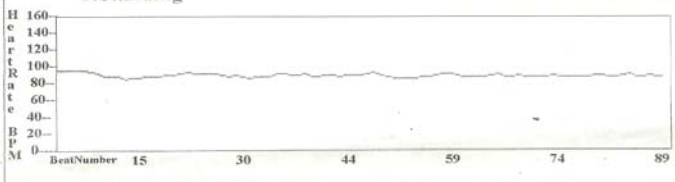
1.Resting Heart Rate : **83 BPM** **GRADE 0**

2.Deep Breathing



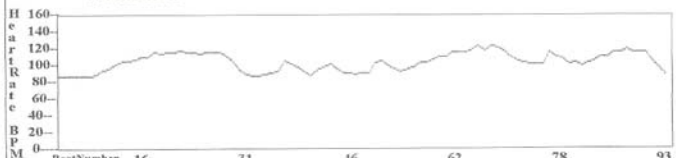
(i).Std.Deviation : 4.99 sec
(ii).Co_Efficient : 4.67%
(iii).E/I Ratio : 1.25
(Normal value > 1.21)
GRADE 0

3.Standing



(i).Std.Deviation : 2.64 sec
(ii).Co_Efficient : 2.49%
(iii).30:15 Stand Ratio=0.99
(Normal Value > 1.03)
GRADE 2

4.Valsalva



(i).Std.Deviation : 45.4 sec
(ii).Co_Efficient : 45.85%
(iii).Valsalva Ratio = 5.3
(Normal value > 1.2)
GRADE 0

SYMPATHETIC FUNCTION

1.Postural Hypotension

BP:Supine	126 / 84 mmHg
BP:Standing immediate	127 / 94 mmHg
After 60 second	127 / 94 mmHg
Change in Systolic BP	1 mmHg

GRADE 0

2.Sustained Hand Grip

Before Grip	130 / 94 mmHg
After Grip	143 / 100 mmHg
Holding Time	117 seconds
Change in Diastolic BP	6 mmHg

GRADE 2

Impression
Early ParaSympathetic Involvement
Definite Sympathetic Involvement
Definite CANS Dysfunction Study
This may be clinically correlated [0-Normal,1-BorderLine,2-Abnormal]

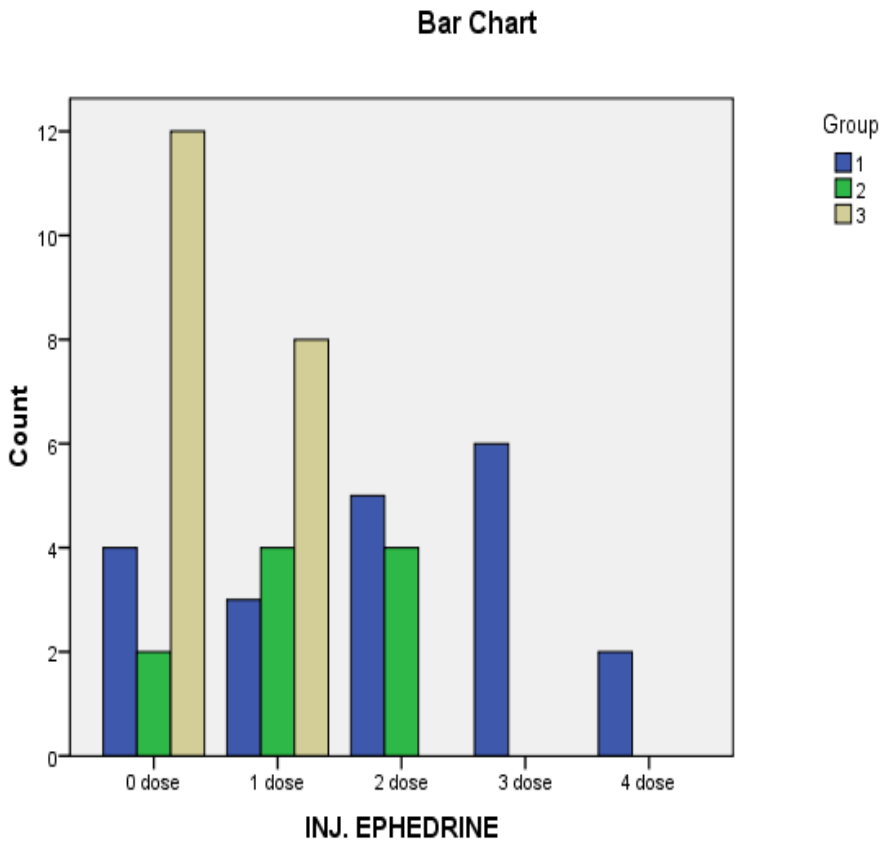
DR.C.R.ANAND MOSES
DIABETOLOGIST

STATISTICAL ANALYSIS:

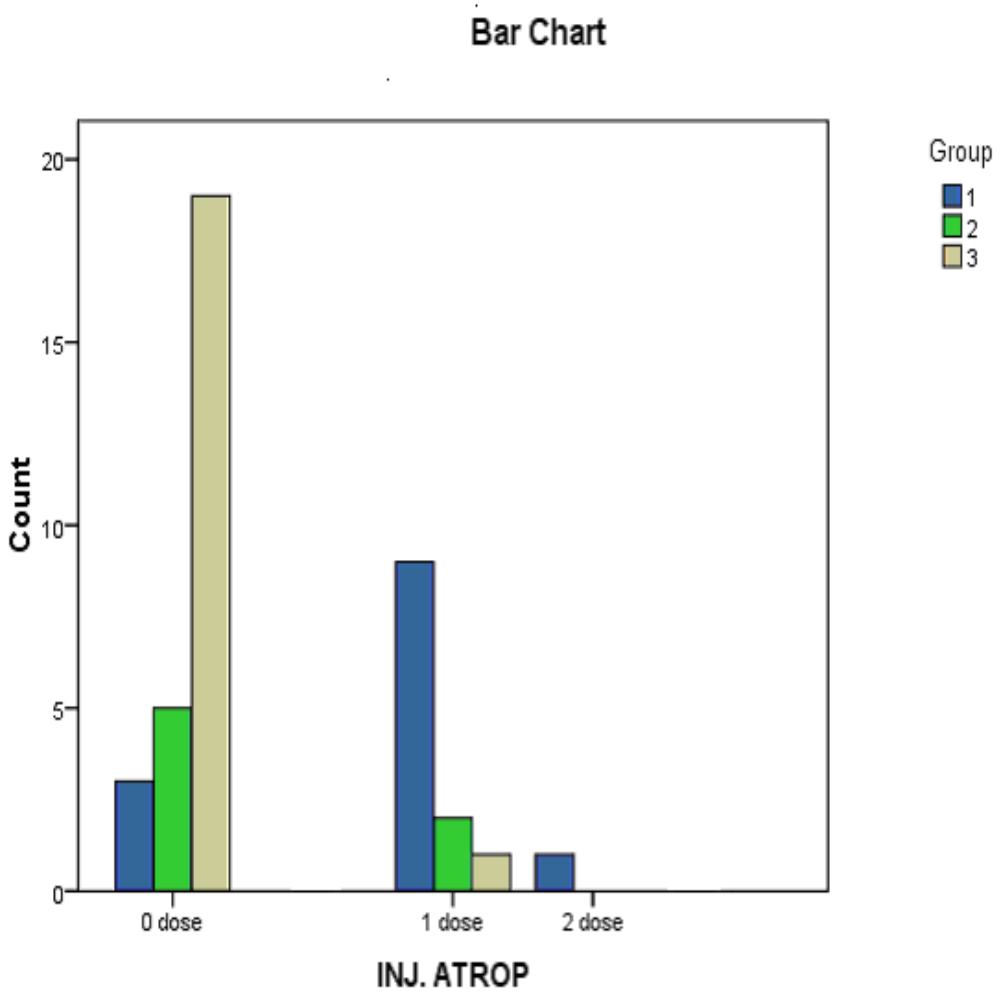
Variables were analyzed with ANOVA and POST HOC test.

INJ. EPHEDRINE * Group Cross tabulation

			Group			
			1	2	3	Total
INJ. EPHEDRINE	0 dose	Count	4	2	12	18
		% within Group	20.0%	20.0%	60.0%	36.0%
	1 dose	Count	3	4	8	15
		% within Group	15.0%	40.0%	40.0%	30.0%
	2 dose	Count	5	4	0	9
		% within Group	25.0%	40.0%	.0%	18.0%
	3 dose	Count	6	0	0	6
		% within Group	30.0%	.0%	.0%	12.0%
	4 dose	Count	2	0	0	2
		% within Group	10.0%	.0%	.0%	4.0%
	Total	Count	20	10	20	50
		% within Group	100.0%	100.0%	100.0%	100.0%


Bar Chart
Group
1
2
3
Count
0
2
4
6
8
10
12
0 dose
1 dose
2 dose
3 dose
4 dose
INJ. EPHEDRINE

INJ. ATROP * Group Cross tabulation						
			Group			
			1	2	3	Total
INJ. ATROP	0 dose	Count	3	5	19	27
		% within Group	15.0%	50.0%	95.0%	54.0%
	0dose	Count	0	3	0	3
		% within Group	.0%	30.0%	.0%	6.0%
	1 dose	Count	9	2	1	12
		% within Group	45.0%	20.0%	5.0%	24.0%
	2 dose	Count	1	0	0	1
		% within Group	5.0%	.0%	.0%	2.0%
	nil	Count	7	0	0	7
		% within Group	35.0%	.0%	.0%	14.0%
	Total	Count	20	10	20	50
		% within Group	100.0%	100.0%	100.0%	100.0%


Bar Chart
Group
1
2
3
Count
20
15
10
5
0
0 dose
1 dose
2 dose
INJ. ATROP

Descriptives					
		N	Mean	Std. Deviation	Std. Error
0 MINUTES SYSTOLIC	1	20	122.60	12.245	2.738
	2	10	125.60	10.617	3.357
	3	20	119.30	10.121	2.263
	Total	50	121.88	11.150	1.577
5 MINUTES SYSTOLIC	1	20	120.90	11.021	2.464
	2	10	120.60	10.834	3.426
	3	20	115.60	8.647	1.934
	Total	50	118.72	10.212	1.444
10 MINUTES SYSTOLIC	1	20	112.70	11.952	2.673
	2	10	117.20	12.155	3.844
	3	20	113.30	7.349	1.643
	Total	50	113.84	10.316	1.459
	Total	5214.720		49	

ANOVA			
		F	**Sig.**
0 MINUTES SYSTOLIC	Between Groups	1.140	.328
5 MINUTES SYSTOLIC	Between Groups	1.597	.213
10 MINUTES SYSTOLIC	Between Groups	.671	.516

ANOVA			
		F	**Sig.**
0 MINUTES DIASTOLIC	Between Groups	2.474	.095
5 MINUTES DIASTOLIC	Between Groups	5.373	.008
10 MINUTES DIASTOLIC	Between Groups	.665	.519

Descriptives					
		N	**Mean**	**Std. Deviation**	**Std. Error**
0 MINUTES DIASTOLIC	1	20	78.80	7.523	1.682
	2	10	75.40	9.143	2.891
	3	20	73.70	6.062	1.355
	Total	50	76.08	7.548	1.067
5 MINUTES DIASTOLIC	1	20	78.50	6.354	1.421
	2	10	75.20	8.121	2.568
	3	20	72.30	4.118	.921
	Total	50	75.36	6.496	.919
10 MINUTES DIASTOLIC	1	20	73.50	9.528	2.131
	2	10	71.80	8.351	2.641
	3	20	70.70	4.824	1.079
	Total	50	72.04	7.658	1.083

Post Hoc Tests

Multiple Comparisons					
LSD					
Dependent Variable	**(I) Group**	**(J) Group**	**Mean Difference (I-J)**	**Std. Error**	**Sig.**
5 MINUTES DIASTOLIC	1	2	3.300	2.317	.161
		3	6.200*	1.892	.002
	2	1	-3.300	2.317	.161
		3	2.900	2.317	.217
	3	1	-6.200*	1.892	.002
		2	-2.900	2.317	.217

Descriptives					
		N	Mean	Std. Deviation	Std. Error
15 MINUTES SYSTOLIC	1	20	103.30	12.057	2.696
	2	10	107.00	10.467	3.310
	3	20	108.20	8.703	1.946
	Total	50	106.00	10.537	1.490
15 MINUTES DIASTOLIC	1	20	67.00	11.617	2.598
	2	10	69.20	9.004	2.847
	3	20	67.10	5.170	1.156
	Total	50	67.48	8.851	1.252

ANOVA			
		F	**Sig.**
15 MINUTES SYSTOLIC	Between Groups	1.144	.327
15 MINUTES DIASTOLIC	Between Groups	.229	.796

Descriptives

		N	**Mean**	**Std. Deviation**	**Std. Error**
20 MINUTES SYSTOLIC	1	20	103.90	9.915	2.217
	2	10	100.00	9.707	3.070
	3	20	102.40	7.989	1.786
	Total	50	102.52	9.069	1.283
20 MINUTES DIASTOLIC	1	20	66.35	10.028	2.242
	2	10	60.20	9.543	3.018
	3	20	63.50	6.833	1.528
	Total	50	63.98	8.895	1.258

ANOVA			
		F	**Sig.**
20 MINUTES SYSTOLIC	Between Groups	.609	.548
20 MINUTES DIASTOLIC	Between Groups	1.688	.196

Descriptives					
		N	**Mean**	**Std. Deviation**	**Std. Error**
25 MINUTES SYSTOLIC	1	20	106.20	8.383	1.874
	2	10	102.60	8.746	2.766
	3	20	99.20	7.266	1.625
	Total	50	102.68	8.472	1.198
25 MINUTES DIASTOLIC	1	20	66.30	8.736	1.954
	2	10	63.60	6.586	2.083
	3	20	60.30	7.263	1.624
	Total	50	63.36	8.086	1.143

Post Hoc Tests

Multiple Comparisons					
LSD					
Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
25 MINUTES SYSTOLIC	1	2	3.600	3.108	.253
		3	7.000*	2.538	.008
	2	1	-3.600	3.108	.253
		3	3.400	3.108	.280
	3	1	-7.000*	2.538	.008
		2	-3.400	3.108	.280
25 MINUTES DIASTOLIC	1	2	2.700	3.012	.375
		3	6.000*	2.459	.019
	2	1	-2.700	3.012	.375
		3	3.300	3.012	.279
	3	1	-6.000*	2.459	.019
		2	-3.300	3.012	.279
*. The mean difference is significant at the 0.05 level.					

Descriptives					
		N	Mean	Std. Deviation	Std. Error
30 MINUTES SYSTOLIC	1	20	104.90	8.296	1.855
	2	10	105.60	5.562	1.759
	3	20	102.40	7.989	1.786
	Total	50	104.04	7.682	1.086
30 MINUTES DIASTOLIC	1	20	66.00	7.894	1.765
	2	10	64.40	6.518	2.061
	3	20	64.20	5.540	1.239
	Total	50	64.96	6.679	.945

ANOVA			
		F	Sig.
30 MINUTES SYSTOLIC	Between Groups	.780	.464
30 MINUTES DIASTOLIC	Between Groups	.397	.675

Descriptives					
		N	Mean	Std. Deviation	Std. Error
45 MINUTES SYSTOLIC	1	20	101.20	8.345	1.866
	2	10	105.00	11.005	3.480
	3	20	108.30	5.777	1.292
	Total	50	104.80	8.514	1.204
45 MINUTES DIASTOLIC	1	20	63.10	9.301	2.080
	2	10	63.40	11.316	3.578
	3	20	69.20	3.518	.787
	Total	50	65.60	8.408	1.189

ANOVA			
		F	**Sig.**
45 MINUTES SYSTOLIC	Between Groups	3.891	.027
45 MINUTES DIASTOLIC	Between Groups	3.354	.044

Post Hoc Tests

Multiple Comparisons					
LSD					
Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
45 MINUTES SYSTOLIC	1	2	-3.800	3.119	.229
		3	-7.100*	2.546	.008
	2	1	3.800	3.119	.229
		3	-3.300	3.119	.295
	3	1	7.100*	2.546	.008
		2	3.300	3.119	.295
45 MINUTES DIASTOLIC	1	2	-.300	3.110	.924
		3	-6.100*	2.540	.020
	2	1	.300	3.110	.924
		3	-5.800	3.110	.068
	3	1	6.100*	2.540	.020
		2	5.800	3.110	.068
*. The mean difference is significant at the 0.05 level.					

Descriptives					
		N	Mean	Std. Deviation	Std. Error
1 HOUR SYSTOLIC	1	20	103.00	10.413	2.328
	2	10	108.60	5.502	1.740
	3	20	109.20	3.750	.839
	Total	50	106.60	7.869	1.113
1 HOUR DIASTOLIC	1	20	62.10	8.447	1.889
	2	10	65.20	5.827	1.843
	3	20	70.10	3.210	.718
	Total	50	65.92	7.148	1.011

ANOVA

		F	Sig.
1 HOUR SYSTOLIC	Between Groups	3.927	.026
1 HOUR DIASTOLIC	Between Groups	8.180	.001

Post hoc test : Multiple Comparisons					
LSD					
Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
1 HOUR SYSTOLIC	1	2	-5.600	2.880	.058
		3	-6.200*	2.352	.011
	2	1	5.600	2.880	.058
		3	-.600	2.880	.836
	3	1	6.200*	2.352	.011
		2	.600	2.880	.836
1 HOUR DIASTOLIC	1	2	-3.100	2.435	.209
		3	-8.000*	1.988	.000
	2	1	3.100	2.435	.209
		3	-4.900*	2.435	.050
	3	1	8.000*	1.988	.000
		2	4.900*	2.435	.050
*. The mean difference is significant at the 0.05 level.					

Descriptives

		N	Mean	Std. Deviation	Std. Error
1.15 HOUR SYSTOLIC	1	20	103.50	10.971	2.453
	2	10	106.40	10.575	3.344
	3	20	111.10	5.562	1.244
	Total	50	107.12	9.546	1.350
1.15 HOUR DIASTOLIC	1	20	64.40	10.455	2.338
	2	10	64.20	8.456	2.674
	3	20	71.30	3.389	.758
	Total	50	67.12	8.477	1.199

ANOVA

		F	Sig.
1.15 HOUR SYSTOLIC	Between Groups	3.537	.037
1.15 HOUR DIASTOLIC	Between Groups	4.660	.014

Post Hoc Tests

Multiple Comparisons					
LSD					
Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
1.15 HOUR SYSTOLIC	1	2	-2.900	3.519	.414
		3	-7.600*	2.874	.011
	2	1	2.900	3.519	.414
		3	-4.700	3.519	.188
	3	1	7.600*	2.874	.011
		2	4.700	3.519	.188
1.15 HOUR DIASTOLIC	1	2	.200	3.062	.948
		3	-6.900*	2.500	.008
	2	1	-.200	3.062	.948
		3	-7.100*	3.062	.025
	3	1	6.900*	2.500	.008
		2	7.100*	3.062	.025
*. The mean difference is significant at the 0.05 level.					

Descriptives

		N	Mean	Std. Deviation	Std. Error
1.30 HOUR SYSTOLIC	1	20	107.80	7.281	1.628
	2	10	112.00	5.657	1.789
	3	20	111.40	5.315	1.189
	Total	50	110.08	6.401	.905
1.30 HOUR DIASTOLIC	1	20	69.50	9.035	2.020
	2	10	69.00	6.683	2.113
	3	20	71.70	2.993	.669
	Total	50	70.28	6.689	.946

ANOVA

		F	Sig.
1.30 HOUR SYSTOLIC	Between Groups	2.254	.116
1.30 HOUR DIASTOLIC	Between Groups	.762	.472

Descriptives

		N	Mean	Std. Deviation	Std. Error
1.45 HOUR SYSTOLIC	1	20	108.90	6.274	1.403
	2	10	115.00	5.354	1.693
	3	20	112.40	5.134	1.148
	Total	50	111.52	6.028	.852
1.45 HOUR DIASTOLIC	1	20	69.40	6.524	1.459
	2	10	71.20	7.254	2.294
	3	20	71.50	2.743	.613
	Total	50	70.60	5.485	.776

ANOVA

		F	Sig.
1.45 HOUR SYSTOLIC	Between Groups	4.272	.020
1.45 HOUR DIASTOLIC	Between Groups	.801	.455

Post Hoc Tests

Multiple Comparisons

LSD

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
1.45 HOUR SYSTOLIC	1	2	-6.100*	2.193	.008
		3	-3.500	1.790	.057
	2	1	6.100*	2.193	.008
		3	2.600	2.193	.242
	3	1	3.500	1.790	.057
		2	-2.600	2.193	.242
1.45 HOUR DIASTOLIC	1	2	-1.800	2.133	.403
		3	-2.100	1.741	.234
	2	1	1.800	2.133	.403
		3	-.300	2.133	.889
	3	1	2.100	1.741	.234
		2	.300	2.133	.889

*. The mean difference is significant at the 0.05 level.

Descriptives

		N	Mean	Std. Deviation	Std. Error
2 HOUR SYSTOLIC	1	20	110.80	5.248	1.173
	2	10	115.80	4.566	1.444
	3	20	112.50	5.021	1.123
	Total	50	112.48	5.261	.744
2 HOUR DIASTOLIC	1	20	72.70	6.465	1.446
	2	10	73.40	5.816	1.839
	3	20	70.80	2.783	.622
	Total	50	72.08	5.158	.729

ANOVA

		F	Sig.
2 HOUR SYSTOLIC	Between Groups	3.292	.046
2 HOUR DIASTOLIC	Between Groups	1.092	.344

Post Hoc Test

Multiple Comparisons

LSD

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
2 HOUR SYSTOLIC	1	2	-5.000*	1.949	.014
		3	-1.700	1.591	.291
	2	1	5.000*	1.949	.014
		3	3.300	1.949	.097
	3	1	1.700	1.591	.291
		2	-3.300	1.949	.097
2 HOUR DIASTOLIC	1	2	-.700	1.994	.727
		3	1.900	1.628	.249
	2	1	.700	1.994	.727
		3	2.600	1.994	.199
	3	1	-1.900	1.628	.249
		2	-2.600	1.994	.199

*. The mean difference is significant at the 0.05 level.

Descriptives

		N	Mean	Std. Deviation	Std. Error
0 MINUTES PULSE RATE	1	20	82.90	10.254	2.293
	2	10	80.60	7.183	2.272
	3	20	77.60	6.443	1.441
	Total	50	80.32	8.491	1.201
5 MINUTES PULSE RATE	1	20	81.20	8.269	1.849
	2	10	77.00	7.257	2.295
	3	20	78.00	5.912	1.322
	Total	50	79.08	7.275	1.029

ANOVA

		F	Sig.
0 MINUTES PULSE RATE	Between Groups	2.038	.142
5 MINUTES PULSE RATE	Between Groups	1.509	.232

Descriptives

		N	Mean	Std. Deviation	Std. Error
10 MINUTES PULSE RATE	1	20	80.90	9.279	2.075
	2	10	77.00	5.907	1.868
	3	20	78.45	6.901	1.543
	Total	50	79.14	7.788	1.101
15 MINUTES PULSE RATE	1	20	78.15	8.431	1.885
	2	10	77.70	4.322	1.367
	3	20	77.75	7.636	1.707
	Total	50	77.90	7.324	1.036

ANOVA

		F	Sig.
10 MINUTES PULSE RATE	Between Groups	.965	.388
15 MINUTES PULSE RATE	Between Groups	.019	.981

Post Hoc Tests

Multiple Comparisons

LSD

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
10 MINUTES PULSE RATE	1	2	3.900	3.018	.203
		3	2.450	2.465	.325
	2	1	-3.900	3.018	.203
		3	-1.450	3.018	.633
	3	1	-2.450	2.465	.325
		2	1.450	3.018	.633
15 MINUTES PULSE RATE	1	2	.450	2.895	.877
		3	.400	2.364	.866
	2	1	-.450	2.895	.877
		3	-.050	2.895	.986
	3	1	-.400	2.364	.866
		2	.050	2.895	.986

Descriptives

		N	Mean	Std. Deviation	Std. Error
20 MINUTES PULSE RATE	1	20	76.50	10.425	2.331
	2	10	75.40	5.582	1.765
	3	20	77.30	6.027	1.348
	Total	50	76.60	7.902	1.118
25 MINUTES PULSE RATE	1	20	78.40	12.133	2.713
	2	10	75.90	3.957	1.251
	3	20	77.30	5.805	1.298
	Total	50	77.46	8.596	1.216

ANOVA

		F	Sig.
20 MINUTES PULSE RATE	Between Groups	.189	.829
25 MINUTES PULSE RATE	Between Groups	.279	.758

Descriptives

		N	Mean	Std. Deviation	Std. Error
30 MINUTES PULSE RATE	1	20	77.40	12.696	2.839
	2	10	71.90	5.174	1.636
	3	20	76.55	7.141	1.597
	Total	50	75.96	9.568	1.353
45 MINUTES PULSE RATE	1	20	78.30	13.223	2.957
	2	10	70.40	10.824	3.423
	3	20	78.55	6.716	1.502
	Total	50	76.82	10.832	1.532

ANOVA

		Sum of Squares	df	Mean Square
30 MINUTES PULSE RATE	Between Groups	213.270	2	106.635
	Within Groups	4272.650	47	90.907
	Total	4485.920	49	
45 MINUTES PULSE RATE	Between Groups	515.830	2	257.915
	Within Groups	5233.550	47	111.352
	Total	5749.380	49	

ANOVA

		F	Sig.
30 MINUTES PULSE RATE	Between Groups	1.173	.318
45 MINUTES PULSE RATE	Between Groups	2.316	.110

		N	Mean	Std. Deviation	Std. Error
1.15 HOUR PULSE RATE	1	20	82.90	11.116	2.486
	2	10	78.10	5.971	1.888
	3	20	77.05	4.893	1.094
	Total	50	79.60	8.444	1.194
1.30 HOUR PULSE RATE	1	20	81.90	10.021	2.241
	2	10	76.60	6.802	2.151
	3	20	77.20	6.271	1.402
	Total	50	78.96	8.283	1.171

ANOVA

		F	Sig.
1.15 HOUR PULSE RATE	Between Groups	2.786	.072

ANOVA

		F	Sig.
1.15 HOUR PULSE RATE	Between Groups	2.786	.072
1.30 HOUR PULSE RATE	Between Groups	2.223	.120

Descriptives

1 HOUR PULSE RATE

	N	Mean	Std. Deviation	Std. Error		
1	20	81.90	13.970	3.124		
2	10	80.30	8.845	2.797		
3	20	77.90	5.046	1.128		
Total	50	79.98	10.159	1.437		

ANOVA

1 HOUR PULSE RATE

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	161.280	2	80.640	.774	.467
Within Groups	4895.700	47	104.164		
Total	5056.980	49			

Descriptives

		N	Mean	Std. Deviation	Std. Error
1.45 HOUR PULSE RATE	1	20	80.75	8.711	1.948
	2	10	77.20	3.795	1.200
	3	20	77.30	6.062	1.355
	Total	50	78.66	7.021	.993
2 HOUR PULSE RATE	1	20	82.60	7.870	1.760
	2	10	76.60	5.254	1.661
	3	20	77.40	5.623	1.257
	Total	50	79.32	6.982	.987

ANOVA

		F	Sig.
1.45 HOUR PULSE RATE	Between Groups	1.508	.232
2 HOUR PULSE RATE	Between Groups	4.209	.021

Post Hoc Tests

Multiple Comparisons

LSD

Dependent Variable	(I) Group	(J) Group	Mean Difference (I-J)	Std. Error	Sig.
2 HOUR PULSE RATE	1	2	6.000*	2.543	.023
		3	5.200*	2.076	.016
	2	1	-6.000*	2.543	.023
		3	-.800	2.543	.754
	3	1	-5.200*	2.076	.016
		2	.800	2.543	.754

*. The mean difference is significant at the 0.05 level.

RESULTS

In group I, during spinal anesthesia, the fall in B.P was more frequent (75%) and they need more doses of inj. Ephedrine (42%) and 33 % patient in group I are non reactive to inj. Ephedrine and they need inotropic support for B.P stability. 5 patients in group I have abnormal results i.e grade II in all five test of autonomic function study .Those five patients were non responsive to inj. ephedrine during hypotensive reactions .They need inotropic support for hemodynamic stability . The occurrence of bradycardia (50%) during hypotensive reaction is also frequent and need atropine(40%).In group II ,fall in B.P was frequent(40%)but less than group I and more frequent than group III. In group III fall in B.P was less frequent (18%) and need less doses of inj. Ephedrine (15%).Fall in B.P can be managed even with i.v fluids in most cases .hypotensive reactions are less frequently accompanied with bradycardia(10%).From the ANOVA and POST HOC tset we can find a significant difference in systolic and diastolic B.P between group I and GROUP III. But there was less significant difference in B.P between group I and groupII ,group II and group III. From ANOVA we find significant difference in pulse rate between group I , II , III at various time interval during intra – operatively.

DISCUSSION

Results of this study indicate that fall in B.P and bradycardia are more frequent in group I than group II and group III. This indicates that diabetic patients with cardiac neuropathy are more liable for hemodynamic variability than diabetes patients without cardiac neuropathy and non diabetic without cardiac neuropathy. Diabetes patients with abnormal (grade 2) in all five autonomic dysfunction need inotropic support for B.P stability. Perhaps the most important things we can do for our patients with diabetes are to make them aware of autonomic neuropathy ,to let them know whether they have it and to help them keep blood sugar level in an acceptable range and explain the risk during regional anesthesia. Doing so not only help to reduce the risk of intra-operative morbidity and mortality but also lower the risk of heart disease ,diabetic eye ,kidney and nerve disease ,each of which patient dearly want to avoid. With a brief 15 minutes autonomic study we can anticipate the risk during anesthesia and can help patients live longer, healthier lives.

CONCLUSION

1. We found a significant correlation between degree of autonomic dysfunction and largest drop in B.P variability in heart rate and rhythm
2. These results prove atypical hemodynamic behavior and extreme B.P instability in diabetes patients with cardiac autonomic neuropathy
3. Therefore we consider it to be very helpful to check the cardiovascular reflectory status of diabetes patient pre-operatively ,so that we can anticipate the risk during anesthesia in such patients

PROFORMA

Group : 1 2 3

Name :

Age : Sex :

I.P. No. :

Unit :

Diagnosis :

Surgical procedure :

Pre- operative Examination :

Routine H/O

Height

Weight

Pulse rate

B.P

R.R.

C.V.S.

R.S

Investigations:

Hb%

Blood sugar

Serum Urea

Serum Creatinine

B.T

C.T.

ASA – PS Grade :

Procedure:

Intravenous fluid replacement :

	B.P			Pulse Rate/rhythm	ECG Rate/rhythm
	systolic	**diastolic**	**mean**		
Every 5 mins for 30 mins					
Every 15 mins till the end of the surgery					

Blood no. of units used :

Post-operative vitals:

BIBILIOGRAPHY

1. **Vinik AI ,Freeman R ,Erbas T** 2003 diabetic autonomic neuropathy semin neurol 23: 365 – 375 (gold ref) [med line]
2. **Ziegler D 1999** cardiovascular autonomic neuropathy :clinical manifestations and measurement diabetes review 7: 342 0-357\
3. **Knuttgen D ,BUTTER –BELZ** u ,gernot A doetin M 1990 unstable blood pressure during anesthesia in diabetes patients with autonomic neuropathy anasth intensivther notfallmed 25 ; 256- 262 [medline]
4. **Ralene E.** maser and james lenbard the jornal of clinical endocrinology and metabolis vol 90 2005 – cardiovascular autonomic neuropathy due to diabetes mellitusclinical manifestation, consequences and treatment.
5. **Lynda A.scott Disprad [D] [NM] [RT] and peter L.kench ,BAPPSE** jornal of nuclear medicine technology vol 32 2004 – cardiac autonomic neuropathy in diabetes patient does I 123 image have a role to play in early diagnosis
6. Diabetes induced cardiac autonomic neuropathy gwharden .com posted by scott w ,**harden dec.2008**.
7. **Ewing DJ ,Clarke BF** ,diabetic autonomic neuropathy clinical manifestations and measurement diabetic review 1999 :& :300 –315
8. **Pfiefer MA Weinberg CR , cook DL** et al ,autonomic neural dysfuntion in recently diagnosed diabetic subjects

9. **Task force of the European society of cardiology** and north American society of pacing and electrophysiology , heart rate variabilitystandards of measurement, physiology interpretation and clinical use .circulation 1996 93 1043-1065
10. **Neil HA ,Thompson AV ,john S** , Mc carthyST ,mann JI diabetic autonomic neuropathy , the gheart rate variability in a geographically defined population diabetes med 1989 6 20 –24\
11. **Sztajzel J 2004** heart rate variability :a non invasive electrocardiographic method to measure the autonomic nervous system. Swiss med wkly 134 514- 522 {med line] 1
12. **Latson TW ,ashmore TH .Reinhart DJ ,klein KW ,giesecke AH 1994** autonomic reflex dysfunction in patients presenting for elective surgery is associated with hypotension after anesthesia induction anesthesiology 80 326 –337 [cross ref } [medline]
13. **Genovely H , pfeifer MA 1988** R-r variation : autonomic test of choice in diabetes .diabetes metab rev 4 : 255 – 271 [medline]
14. **Kahn R 1992** proceeding of a consensus development conference on standardized measure in diabetic neuropathy autonomic nervous system testing diabetic care 15 :1095 –1103 [medline] 70:591–597[CrossRef][Medline]

15. **Knuttgen D, Buttner-Belz U, Gernot A, Doehn M** 1990 Unstable blood pressure during anesthesia in diabetic patients with autonomic neuropathy. Anasth Intensivther Notfallmed 25:256–262[Medline]
16. **Latson TW, Ashmore TH, Reinhart DJ, Klein KW, Giesecke AH** 1994 Autonomic reflex dysfunction in patients presenting for elective surgery is associated with hypotension after anesthesia induction. Anesthesiology 80:326–337[CrossRef][Medline]
17. **Kitamura A, Hoshino T, Kon T, Ogawa R** 2000 Patients with diabetic neuropathy are at risk of a greater intraoperative reduction in core temperature. Anesthesiology 92:1311–1318[CrossRef][Medline]
18. **Sobotka PA, Liss HP, Vinik AI** 1986 Impaired hypoxic ventilatory drive in diabetic patients with autonomic neuropathy. J Clin Endocrinol Metab 62:658–663[Abstract/Free Full Text]
19. **Keyl C, Lemberger P, Palitzsch KD, Hochmuth K, Liebold A, Hobbhahn J** 1999 Cardiovascular autonomic dysfunction and hemodynamic response to anesthetic induction in patients with coronary artery disease and diabetes mellitus. Anesth Analg 88:985–991[Abstract/Free Full Text]
20. **Purewal TS, Watkins PJ** 1995 Postural hypotension in diabetic autonomic neuropathy: a review. Diabet Med 12:192–200[Medline]

21. **Pfeifer MA** 1990 Cardiovascular autonomic neuropathy: advances in testing help unlock its complexity. Diabetes Spectrum 3:45–48

22. **Shakespeare CF, Katritsis D, Crowther A, Cooper IC, Coltart JD, Webb-Peploe MM** 1994 Differences in autonomic nerve function in patients with silent and symptomatic myocardial ischemia. Br Heart J 71:22–29[Abstract/Free Full Text]

23. **Rosen SD, Camici PG** 2000 The brain-heart axis in the perception of cardiac pain: the elusive link between ischemia and pain. Ann Med 32:350–364[Medline]

24. **Airaksinen KEJ** 2001 Silent coronary artery disease in diabetes—a feature of autonomic neuropathy or accelerated atherosclerosis? Diabetologia 44:259–266[CrossRef][Medline]

25. **Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, Taillefer R, Wittlin SD, Heller GV, Filipchuk N, Engel S, Ratner RE, Iskandrian AE, for the Detection of Ischemia in Asymptomatic Diabetics (DIAD) Investigators** 2004 Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 27:1954–1961[Abstract/Free Full Text]

Group 1 diabetic with peripheral neuropathy														
Sl.No	0 min sys 0 min dia		5 min sys	5 min dias	10 minsys	10 min dia	15 min sys	15 min dias20 min sy		20 min dia	25 min sys	25 min dia	30 min sys	30 min dia
1	130	70	130	70	100	60	90	56	110	64	108	64	108	64
2	110	80	110	80	90	54	120	80	110	70	112	74	112	76
3	120	80	120	84	120	86	116	84	114	80	110	74	120	76
4	112	66	108	66	108	66	94	56	88	52	100	62	100	60
5	126	84	124	80	130	84	124	86	110	84	114	84	112	76
6	128	84	124	84	116	82	110	82	110	82	118	84	108	82
7	118	86	114	82	110	82	94	58	100	58	96	54	98	56
8	114	74	116	76	116	74	106	64	104	69	108	66	108	70
9	136	84	134	84	124	80	100	72	92	56	100	64	94	60
10	100	72	100	70	94	64	92	64	110	78	102	68	100	64
11	110	68	110	70	108	69	100	56	92	62	90	60	88	54
12	128	86	124	84	126	86	120	76	106	72	100	64	88	54
13	110	74	108	74	110	73	90	58	120	74	116	70	110	72
14	122	76	128	82	120	76	114	74	114	70	120	74	114	74
15	140	86	138	86	134	84	100	64	90	52	108	68	104	62
16	110	68	110	70	104	68	104	70	106	68	110	64	104	64
17	130	84	126	78	108	70	92	60	84	52	106	64	104	66
18	124	76	124	80	100	60	90	52	108	64	110	56	106	64
19	148	92	140	86	110	72	90	48	110	60	106	62	110	64
20	136	86	130	84	126	80	120	80	100	60	90	50	110	62
sGroup 1 diabetic with peripheral neuropathy														
Sl.no	45 m sys	45 min dia	1 h sys	1 h dia	1.15 sys	1.15 dia	1.30 sys	1.30 dia	1.45 sys	1.45 dia	2 h sys	2 h dia	0 min p.r	5 min p.r
1	94	56	114	70	110	70	110	70	120	74	120	74	86	90
2	100	68	92	54	110	68	116	74	124	72	124	84	98	92
3	100	60	94	50	124	84	114	78	116	76	118	82	74	76
4	100	62	104	64	106	64	110	68	108	66	104	66	86	84
5	114	76	118	76	118	90	110	82	114	80	110	76	94	96
6	92	52	106	64	116	74	118	76	108	72	112	84	92	86
7	106	68	104	56	96	64	108	64	104	64	108	74	84	76
8	110	64	110	70	110	74	108	74	110	78	114	74	68	72
9	90	56	110	64	92	60	102	64	102	64	108	62	98	84

10	96	60	94	62	88	54	108	82	106	76	106	72	68	68
11	106	62	96	62	92	58	106	82	104	64	106	64	74	70
12	108	82	92	60	90	56	94	56	104	66	110	70	68	72
13	112	80	108	74	96	62	88	52	106	68	106	70	89	84
14	120	74	122	74	110	68	110	74	110	76	112	74	90	92
15	92	54	110	62	92	54	106	60	108	64	108	62	92	90
16	100	68	110	64	110	68	108	74	110	74	106	72	86	84
17	96	60	90	54	104	60	106	62	108	62	108	70	76	78
18	92	50	110	66	88	48	106	56	96	54	116	74	68	74
19	100	56	88	50	114	56	120	72	112	70	110	80	88	82
20	96	54	88	46	104	56	108	70	108	68	110	70	79	74

Group 1 diabetic with peripheral neuropathy

Sl.No	10 min p.r	15 min p.r	20 min p.r	25 min p.r	30 min p.r	45 min p.r	1 h p.r	1.15 pr	1.30 p.r	1.45 p.r	2 h p.r	Sex	inj ephedrine	inj atrophine
1	94	84	90	84	90	84	96	92	98	90	92	Male	2 dose	nil
2	96	84	84	80	82	80	88	86	84	90	94	female	2 dose	nil
3	74	78	84	74	72	74	78	76	90	84	84	female	1 dose	nil
4	84	88	88	84	84	80	84	86	90	84	84	Male	1 dose	nil
5	92	84	86	88	84	98	94	96	92	93	92	female	0 dose	nil
6	84	84	86	84	85	82	84	84	90	86	86	Male	1 dose	nil
7	74	76	76	72	68	56	92	86	88	88	82	female	3 dose	1 dose
8	74	78	74	72	74	74	76	72	72	74	74	female	o dose	nil
9	84	72	74	66	60	54	98	96	90	88	78	Male	3 dose	1 dose
10	70	71	64	58	86	92	78	74	72	74	74	Male	3 dose	1 dose
11	70	68	64	62	56	100	86	82	80	80	78	female	2 dose	1 dose
12	78	72	70	64	56	62	102	74	62	58	98	Male	4 dose	2 dose
13	86	75	74	64	56	98	100	64	66	76	74	female	2 dose	1 dose
14	92	88	80	82	82	82	80	84	88	84	84	Male	0 dose	o dose
15	90	92	88	90	88	74	72	70	70	74	74	female	3 dose	o dose
16	88	80	82	86	88	90	86	92	90	88	90	female	o dose	o dose
17	68	64	56	98	96	68	72	74	78	80	80	Male	3 dose	1 dose
18	72	65	55	104	89	74	66	68	74	66	68	Male	4 dose	1 dose

19	80	90	81	80	84	78	52	100	76	78	84	female	3 dose	1 dose
20	68	70	74	76	68	66	54	102	88	80	82	Male	2 dose	1 dose

Group 2 diabetic without peripheral neuropathy														
Sl.No	0 min sys 0 min dia		5 min sys	5 min dias	10 minsys	10 min dia	15 min sys	15 min dias20 min sy		20 min dia	25 min sys	25 min dia	30 min sys	30 min dia
1	126	78	124	76	120	70	110	68	108	66	100	56	96	56
2	138	88	130	86	130	80	128	72	100	62	88	52	110	74
3	126	76	118	78	110	80	100	76	92	56	110	76	108	58
4	142	84	138	84	138	78	110	78	94	52	110	68	104	56
5	108	72	104	70	100	64	100	68	110	70	108	68	104	68
6	134	86	130	84	124	80	100	76	90	48	110	64	110	70
7	122	74	120	70	118	70	110	62	92	48	110	62	108	64
8	118	70	110	70	112	72	102	68	90	56	88	62	110	68
9	128	68	124	74	120	70	118	76	116	74	100	64	110	70
10	114	58	108	60	100	54	92	48	108	70	102	64	96	60
Group 2 diabetic without peripheral neuropathy														
Sl.no	45 m sys	45 min dia	1 h sys	1 h dia	1.15 sys	1.15 dia	1.30 sys	1.30 dia	1.45 sys	1.45 dia	2 h sys	2 h dia	0 min p.r	5 min p.r
1	92	54	110	54	112	66	116	56	120	72	118	70	76	78
2	108	52	110	58	94	52	112	72	120	78	118	72	80	82
3	110	64	112	68	112	70	120	72	120	72	118	80	92	88
4	92	56	112	64	110	70	118	72	116	70	118	72	86	86
5	110	64	104	68	98	60	106	64	108	64	108	66	74	72
6	120	86	118	74	120	68	118	74	122	80	120	86	76	78
7	112	70	110	70	116	74	110	76	114	78	110	76	70	68
8	108	70	98	64	86	48	104	60	108	56	120	70	78	70
9	112	70	108	68	110	70	108	74	112	74	118	70	84	80
10	86	48	104	64	106	64	108	70	110	68	110	72	90	68
Group 2 diabetic without peripheral neuropathy														
Sl.No	10 min p.r	15 min p.r	20 min p.r	25 min p.r	30 min p.r	45 min p.r	1 h p.r	1.15 pr	1.30 p.r	1.45 p.r	2 h p.r	inj ephedrine i	nj atrophine	Sex
1	76	74	70	72	74	78	80	72	70	76	78	1 dose	0dose	female
2	86	84	80	76	72	70	76	78	72	76	78	2 dose	o dose	male
3	82	80	88	82	80	86	88	82	88	80	82	1 dose	o dose	male
4	84	86	76	78	62	54	98	90	88	80	80	2 dose	1 dose	female
5	70	74	70	77	70	72	70	72	72	72	70	0 dose	0dose	male
6	76	75	70	74	70	76	74	76	74	72	70	1 dose	o dose	male
7	68	78	74	76	72	70	70	72	70	74	70	1 dose	0 dose	female
8	74	74	74	68	67	72	79	75	74	78	74	2 dose	0dose	male
9	80	76	78	76	78	76	80	84	80	82	80	0 dose	0dose	male

10	74	76	74	80	74	50	88	80	78	82	84	2 dose	1 dose	male

Group 3 non diabetic without peripheral neuropathy														
Sl.No	0 min sys 0 min dia		5 min sys	5 min dias	10 minsys	10 min dia	15 min sys	15 min dias20 min sy		20 min dia	25 min sys	25 min dia	30 min sys	30 min dia
1	134	82	130	78	124	74	118	74	118	74	108	70	110	72
2	122	78	118	76	108	80	106	74	100	70	104	72	98	64
3	114	72	112	72	112	68	108	68	108	70	98	60	90	56
4	108	64	106	68	106	76	110	74	102	64	94	58	88	54
5	110	70	110	70	112	72	110	68	104	64	100	60	102	64
6	124	84	118	80	120	78	116	68	110	64	102	66	96	58
7	110	68	108	70	102	64	92	60	88	56	110	58	108	64
8	144	86	138	80	130	74	110	64	98	58	90	54	120	68
9	132	80	128	80	124	74	128	76	108	74	102	60	98	64
10	106	72	104	70	106	72	108	70	98	64	102	60	104	64
11	112	68	108	70	104	68	100	64	94	60	100	64	102	64
12	120	74	118	72	118	76	120	68	110	64	100	60	104	68
13	130	74	116	70	110	70	100	68	94	56	88	50	110	70
14	110	68	108	70	110	64	100	60	98	54	100	58	104	64
15	126	70	120	68	118	64	108	60	104	56	96	54	88	52
16	114	70	112	72	110	70	100	62	94	52	86	46	104	64
17	122	72	120	70	118	70	118	64	116	68	112	68	110	70
18	110	74	110	70	110	68	100	70	98	70	98	68	104	70
19	120	80	112	72	110	64	102	60	96	60	88	50	108	70
20	118	68	116	68	114	68	110	70	110	72	106	70	100	64